Legislating to death

Edgar Alexandre and **Guy Villax** of **Hovione** argue that the impact of legislation on the EU pharmaceutical fine chemicals industry could be to kill it altogether

The European pharmaceutical fine chemicals industry is a major creator of wealth, a major employer and a major net exporter. In 2000, CEFIC reported that the EU trade surplus in pharmaceuticals was €19 billion. It is a high-value, low-volume business that is characterised by a high science content, a profound understanding of its processes and intense regulation. Europe is the cradle of both chemistry and pharmacy and is a powerhouse of pharmaceutical fine chemicals - and yet its future is grim. Why?

About 75% of the APIs in the medicines on the shelves of US pharmacies are manufactured outside the US and over half of them come from Europe. In 1996, 194 of the FDA's 290 foreign inspections (66% of the total) related to APIs. Of those, 131 (45%) took place in Europe (that is, the UK, the Republic of Ireland, Spain, Germany, Italy, France and Switzerland).

Even though the North American pharmaceutical market is much larger than Europe's, it grows at almost double the rate seen in Europe. According to IMS figures of world sales through retail pharmacies, in the twelve months to November 2001 sales in North America grew by 17% to €138.9 billion, while Europe's five main markets grew by 9% to €54.7 billion.

On the other hand Europe's capacity, breadth and depth of know-how and technologies are unrivalled and the EU today enjoys a significant positive trade balance in pharmaceuticals with the rest of the world, including the US.

When the first computer modelled HIV protease inhibitors went into clinical development in the mid-1990s, the only companies outside Big Pharma with cryogenic reactions between –50 and –100˚C - a key technology for these complex molecules, and one backed by innovative chemistry - were essentially European-based. The suppliers were Finorga in France, Newport Synthesis in Ireland, Hovione in both Portugal and Macau and maybe also UBE in Japan.

In biotechnology, because we are losing the race to the Americans, the EU spares no effort to stimulate and support European research efforts, both state and private. Yet in pharmaceutical fine chemicals - an area where Europe is light years ahead of anyone else - the EU is creating through its legislation a stifling environment that provides the industry with the dilemma of locating elsewhere or disappearing.

Help & hindrance

Helpful sectoral legislation in this field often sits side-by-side with unwise, stifling and indiscriminate regulation.

The competitive position of Europe's pharmaceutical fine chemicals industry is subject to an extensive, dense, complex, rigorously supervised body of legislation that is in force at both national and EU levels, at international level from the WHO and the International Conference on Harmonisation (ICH) and in the export markets - the US and Japan.

Industry embraces most of this as a necessary driver for a level playing field but other parts of it appear to be nothing more than a European idiosyncrasy that serves no other practical purpose but to diminish the advantages of a European location. The legislation that is embraced as innovative, common sense and globally harmonised is the part connected with the registration and approval of new pharmaceutical products.

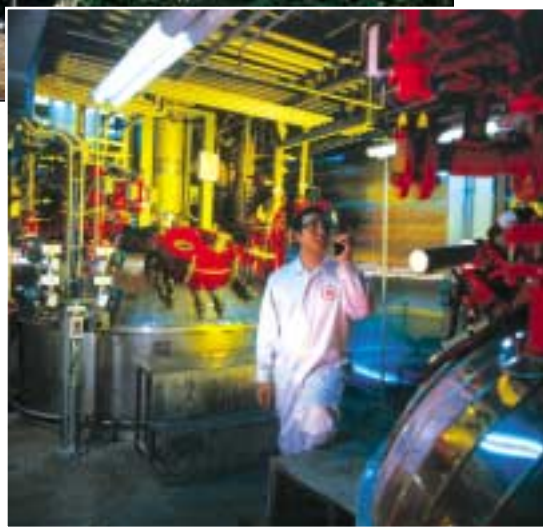
The key examples are the ICH guidelines, which affect the preparation of product specifications, the levels of impurities, the format and standards of stability studies, the minimum standards of GMP during manufacturing operations and so forth. These have been enacted into Guidelines to Industry published in the US Federal Register. Similar guidelines exist in other countries, including Australia, Japan and Switzerland, but not yet in the EU.

The basis for the ICH guidelines is the global standardisation of best practices that have the double aim of facilitating faster and near-simultaneous access to new medicines for patients in all countries and the reduction of costs by avoiding duplication of tests and studies. Their implementation is notable for the degree of collaboration and consultation between the authorities and industry.

Additional components of these internationally harmonised legislative initiatives are the mutual recognition protocols between regulatory authorities and the Common Technical Document (CTD)[1]. This is an internationally agreed format for the preparation of a well-structured presentation for applications to be submitted to the regulatory authorities in the three ICH regions of Europe, the US and Japan. It is intended to save time and resources and to facilitate review and communication.

On the other hand, the last ten years have seen a plethora of legislation in Europe that markedly interferes with the international market and distinctly affects the competitive advantage of the European pharmaceutical fine chemical industry. This has distorted the market and led to companies having to take measures to meet the new legislative demands in ways that are totally opposite to the intent of the legislator. The net effect is that Europe loses jobs, manufacturing capacity, exports and - worst of all - know-how.

The legislation that most distorts the markets is that connected with the process of innovation. The issues that must be addressed include: the supplementary patent certificate (SPC) and the lack of Bolar provision; the exist-



Hovione has diversified away from Europe with its facility in Macau (above and right) **and a new technology transfer centre in New Jersey** (left)

ing and proposed controls of registration, evaluation and authorisation of chemicals (both existing and new); the Integrated Plan for Pollution Control (IPPC); and, the European Pollutant Emission Register (EPER)

In this paper, we will show how the application of this legislation is hurting the European pharmaceutical fine chemicals industry and having an effect opposite to that intended by the legislators. We will also demonstrate that its application within the EU often presents inexplicable inconsistencies.

Generics

Generic drugs are a big and fast growing business. According to Jan Leschly, former CEO of SmithKline Beecham, in the Ernst & Young 2001 report on European Life Sciences, the next ten years will see patent expiries of drugs currently generating some €91 billion/year worth of sales.

The timing and the strategy for the development of a generic pharmaceutical involves being ready with an approved marketing licence on the day the patent expires, so that the product may be put on the market then. This is already the case in the US, Canada, Australia and Israel, where a Bolar provision has been enacted which provides that none of the acts necessary to apply for a marketing license (development work, validation batches, stability and bio-equivalence tests) constitute patent infringement.

In Europe, this is not the case. Anyone who wants to develop a generic drug in Europe will start four to six years too late. Indeed, it takes about two to four years to do the necessary work to develop a manufacturing process and the data for registration and two to three more years after the data is complete for the average EU authority to conclude its review of a generic.

A further EU piece of legislation is the SPC, which exacerbates the lack of Bolar provision, because it extends the life of the patent holder's monopoly beyond patent expiry. The SPC assures the patent holder of effective market exclusivity for 15 years from the first European registration, independent of the patent expiry date. Additional national complexities mean that generics firms in Italy and France are at a particular disadvantage, to the point that a large number of Italian API firms have moved their development and manufacturing capabilities abroad.

Examples of companies driven away because of the uncompetitive generics legislation in Europe include: Sicor, an Italian leader in cancer drugs which now develops its new generic compounds in Mexico; Spain's Esteve Química, which has also invested in development and manufacturing facilities in Mexico; and, Profarmaco and Nordic Synthesis, long-established Italian and Swedish API manufacturers which are now part of the Cambrex group and have built pilot plants in the US.

The generics industry is relatively young and its management style is traditionally entrepreneurial. However, a consolidation process has led to the emergence of several companies whose strategy includes the systematic development of all generic APIs. Teva of Israel, Cambrex of the US, Pliva of Croatia, Apotex of Canada, Ranbaxy of India and Novartis of Switzerland - none of them EU-based - are the leaders. The traditional players, the original builders of this industry, who were usually Italians, are falling by the wayside.

Legislation has not stopped the Europeans from developing generic drugs, it has just pushed them into doing so outside Europe. Those involved in extra-European collaborations in order to avoid the European block on generics development are legion. Dipharma of Italy has now bought a plant in Malta, Hexal and Ratiopharm do some of their development batches in Iceland and a large proportion of the generic versions of Glaxo's Zantac was formulated in Turkey prior to patent expiry in the EU.

South Africa is a common location for bio-equivalence studies. Generics firms in New Zealand have become key players in the process of preparing and filing registration dossiers and then selling these files to the various generics houses - who are soon to become mere distributors, albeit profitable ones.

There is a steady stream of brain- and manufacturing-drain away from Europe in the key skills of developing and registering new generics. Roxythromycin is a typical example of this 'patent tourism'. Aventis's Rulid went off patent in Germany in 2001 and the first registrations to go onto the market were made by a Jordanian firm using an API made by Hovione in Macau.

(In fact, all of the current generic formulations of Roxithromycin contain API from Hovione. We saw the writing on the wall and in 1986 and took the decision to invest in manufacturing capabilities in Macau - away from EU manufacturing regulations and yet compliant with both EU and US registration requirements, thus enabling it to be a key source of APIs for the generic houses and both Big and Small Pharma.)

Meanwhile, the non-European companies grew rich on the know-how imparted to them

by their EU-constrained clients, to the point where they can now venture back into Europe on the acquisition trail. For example, Delta of Iceland acquired Omega Pharma in March 2002 and Pharmaco in August 2002.

The original intent of the legislation was to encourage R&D in Europe. This has failed. A recent Goldman Sachs study reports that only three of the top 20 late stage pipeline drugs are from the EU[2]. There is little doubt that the trend inversion will continue and that the greater number of approved NCEs will come from Small Pharma. Here again - by any measure - the Nasdaq-quoted biotech firms are light years ahead of their European counterparts.

Production & NCEs

The recent EU White Paper for a Future Chemicals Policy has recently caused much stir in the wider industry, though it actually contains little that is really new for the pharmaceutical fine chemicals sector.

The wider industry is concerned with the 'burden of the past' - the 30,000 existing chemicals for which little or no safety and ecotoxicity information had been grandfathered in the European Inventory of Existing Commercial Chemical Substances (EINECS) of 100,106 'existing chemicals' deemed to have been on the EU market between 1 January 1971 and 18 September 1981, and which must either be eliminated from the market or re-registered by 2012.

In pharmaceutical fine chemicals, however, we are at the leading edge of innovation and more concerned with the future, with innovation. Our capability to support the drug development process is being systematically hurt. In the past, whenever a Big Pharma multinational or a small biotech firm from the US needed to outsource some chemical synthesis process, they invariably went to Europe. This is no longer the case and we should ask why, as it could shed some light on the White Paper debate.

Those involved in making chemical APIs have had to cope with the need to register new compounds on the European List of Notified Chemical Substances (ELINCS) and with process-oriented research & development (PORD) derogation applications for some time. This is costly, time-consuming and resource-consuming, it affects the critical path and, at least 90% of the time, it is demonstrably a waste of time.

Making APIs involves complex, multi-step chemistry. The last reactions have to meet rigorous and costly GMP requirements that are subject to quality inspections by the authorities to verify compliance. Naturally, certain raw materials are bought in from other upstream industries with less costly operations, involving numerous purchases, sales and cross-border transactions. The White Paper is proposing that every intermediate, whether isolated or not, must be evaluated and registered.

Even ignoring the intermediates that are made entirely in one plant (isolated or not), on average any new API will need at least one new starting material, if not also a new reagent or a new side-chain. Often the synthesis is convergent, so the number of new chemicals that might be made by a third party could potentially double that number. Thus, for every API you will need about four registrations. The API itself is exempt because it is the object of infinitely more thorough toxicology and safety studies.

Automated cGMP API manufacturing at the main Hovione site in Portugal

An example of a very new science are the computer-modelled HIV compounds. The process for Viracept, for instance, involved putting together three different building blocks that all required ELINCS registration. Viracept was a fast-tracked drug, and a combination of a clever regulatory strategy and unique medical benefits got the FDA to approve the drug in 42 days. Within a year, it was being produced at a volume of 5-10 tonnes/month. The ELINCS process was clearly in the critical path.

Currently, producing 10 kg/year of a chemical triggers the need for registration. Over 90% of APIs made at this scale will never make it to commercial-scale production. Indeed, products often reach clinical demands in excess of 1,000 kg and still fail to gain approval for sale in the market. How can anyone defend the cost, the time and the laboratory animals that are needed for doing toxicology studies on products that never leave the control of experts and that have a statistically proven 90% likelihood of never becoming more than an R&D exercise?

Today, there are about 1,805 drugs in development and awaiting approval at the FDA: 468, 776 and 395 respectively in Phases III, II and I. If these were made exclusively in the EU, they would trigger around 7,200 notifications - about four times more than have been registered in ELINCS since the whole process started in 1994.[3]

(Before this bureaucratic hurdle was imposed on cross-border authorisations at the 10 kg level, Europe benefited from a significant advantage over the US the very early screening of APIs. US law directs that no API can be used for clinical development or exported without an IND being filed. Big Pharma companies exploited a loophole that allowed them to ship the penultimate intermediate to a pharmaceutical chemicals contractor outside the US to process the final API. This required no more than the agreement of an ethical committee and avoided the need for IND filing, thereby also giving Europe a large amount of business at the chemistry level and at the clinical testing and CRO end.)

The chemical development of a new drug is highly controlled and requires expertise, complete traceability and large budgets. This process is already strictly regulated by the health authorities for the final product and requires industrial licensing as well as licensing for personnel protection during manufacture. Moreover, those involved in pharma R&D already face tremendous pressures to exert the best possible control over the products in question.

The small quantities of intermediates required for API manufacture are extremely costly (never under €1,000/kg and often more than €10,000/kg). Each batch is monitored and its quality is controlled to a greater detail than any product in routine production. It is usually shipped by courier or direct air cargo, if not actually hand-carried, and its progress is monitored in Gantt charts by any number of highly paid project managers.

Furthermore, our industry accounts for every kilo with a precision that even SAP software has difficulty in coping with. When called to manufacture controlled substances, like narcotics or psychotropics, it will account for amounts down to the last gram and its managers may face jail sentences for any failures.

The industry already carries out toxicology studies for raw materials and intermediates in order to prepare safety data sheets and assess maximum exposure levels in connection with HSE. What is the point of introducing a further bureaucratic step in the process? And what is the added benefit to public safety in having these registrations imposed on the making of small quantities for R&D purposes that will never reach the public?

Experience shows that the agencies of the EU member states responsible for the authorisa-

tion process are short-staffed. The Portuguese office of the Environment Ministry, for example, has one senior manager and two assistants to manage this and other functions. Their letter of 21 June 2002, asking Hovione not to pressure them to meet deadlines, suggests that they are significantly short of resources.

Across Europe there are inconsistencies: one country has a trigger threshold of 100 kg, another has 10 kg; one country commits to a 30-day delay to reply, another to 60. The '3 Rs' approach laid out in Section 3.3 of the White Paper indicates a commitment to minimise animal experiments, yet experience shows that, at member state level, best use of existing information is not taken into account.

As recently as July 2002, for example, the Portuguese authorities, when faced with an application for a PORD derogation from ELINCS requirements for low quantities used in R&D, took no account of a toxicity study carried out in the PRC, and requested the study to be repeated in the EU. Here again, we would all benefit from international harmonisation of methodology in toxicology studies. The UN Sub-Committee of Experts on the Globally Harmonised System should make an effort to have this tool in place as soon as possible.

The cost of the toxicology work needed for a PORD at the <100 kg quantity is in the region of €10,000/compound, but this is not the only concern. The issue is that the legislation causes companies to meet the requirements in every instance without exception, when common sense would recommend delaying carrying out such tests until after clinical data provides encouraging results in certain cases.

The legislation also introduces an extra item that needs to be considered and which might interfere with the critical path of an R&D project, an item that is outside the control of the business and that requires additional resources to address it. For a company with €100 million/year in sales doing about 20 new APIs/year in different phases of development, the management of PORDs alone requires a full-time person with a budget of €500,000.

Again, the story of roxithromycin sheds light on how the ELINCS is used to create barriers to entry and to create a dominant position in a product, using regulations in a way that the legislators never considered.

Biochemie, an Austrian-based subsidiary of Novartis which makes APIs by fermentation and has a leading position in erythromycines like roxithromycin, applied for and obtained ELINCS registration for oxime, a key intermediate common to the synthesis of roxithromycin, azithromycin and clarithromycin.

Since the EU discourages second and subsequent ELINCS registrations for the same compound, Biochemie now has an apparent monopoly on oxime, which is sold at €100-€200/kg and is consumed at a volume of over 1,000 tonnes/year, making it worth €4 billion at pharmacy prices.

Naturally the rest of the universe will not sit patiently and pay Biochemie a fee; at least one competing producer found another salt of oxime and has registered it as another substance. The next effect is that a known, safe substance has twice been the subject of €350,000 worth of toxicology studies and the same animal tests had to be carried out again.

In our view, then, debate on the wisdom of the White Paper in the area of pharmaceutical fine chemicals, and REACH in particular, should focus on a cost-benefit analysis of everything connected with EINECS, ELINCS and PORDs.[4]

IPPC & EPER

The IPPC legislation is yet another layer of legislation that most companies in the industry believe to be sound and necessary. The format and ***modus operandi*** is, however, flawed and costly. IPPC has been in force in Portugal since August 2000, the application form has 60 pages and an application fills a truck. In Portugal, IPPC is applicable to about 400 factories, which must all must be licensed under it by 2007. To date, only two have done so.

Again, the debate is not whether there ought to be a strict licensing process for our industry but rather whether IPPC is a sound approach for an industry like pharmaceutical fine chemicals that manufactures in multi-purpose, multi-product plants, where flexibility is the name of the game and where it is impossible to predict what products the market will demand in two years time, where new products may require raw materials and technologies not yet invented, where production is in batches and where process improvements may offer significant opportunities for cost reduction from changes in synthetic routes, raw materials or technologies.

IPPC demands that we define all of those parameters before the plant is built. At Hovione, we hardly know with more than 33% probability what products might be produced in it over five years. IPPC, however, requires us to state our forecasts as written commitments. These are then filed with authorities that would appear not to have the resources to process such a large amount of data. On top of that, the data is often confidential and belongs to our customers, which complicates the matter still further.

R&D facilities, it should be added, are specifically excluded from the constraints of IPPC, though their licensing procedure is still labyrinthine, lengthy and frustrating. Hovione decided in 2000 to build two pilot plants one in Portugal (within the existing site at Loures) and one in New Jersey at a greenfield site that had not then been identified.

We filed for the building permit and other licenses in Portugal before we selected the land in New Jersey in December 2000. Our New Jersey pilot plant opened for business last year but the Portuguese one is still waiting for permits.

EPER provides another example of the disparate standards that apply across Europe and is symptomatic of the mind-set of the authorities.

Portuguese industry was instructed to file EPER data on a quarterly basis and for every emission. The EU-issued guidebook stipulated that emissions were to be filed annually and only if the site exceeded defined thresholds. If there are debates on such simple matters, what can we expect when local authorities must define what is a 'low risk' substance - especially when hardly any guidelines are given?

The EU is keen on transparency, it actively promotes disclosure and EPER would enable every neighbour of a plant to see the list of the emitted pollutants.

What should the EU do?

As companies have a greater R&D intensity in their business, so their planning is longer term. Additionally, the chemical industry is very capital-intensive and long-term investment plans are analysed with considerable care. It should therefore not surprise anyone that the legislative efforts by the EU in the last ten years have not gone unnoticed. The trends are clear for all to see.

Europe has not built a new greenfield API site plant for ten years - except possibly the odd Swiss or Japanese API manufacturing facility in the Republic of Ireland. Pharmaceutical multinationals have only one manufacturing strategy: to locate API synthesis in a tax-friendly location. This was first Puerto Rico, later Ireland, and, since Europe has killed the goose that laid the golden egg, Singapore has become the most preferred investment location.

India and China have in the past 20 years addressed the vacuums caused by the EU patent law situation in terms of generics, and have become the emerging location for the intermediates industry. Anyone in Europe who wants to remain in the business is migrating to more favourable locations: Mexico, Canada and the US appear to be the preferred options.

The pharmaceutical fine chemicals sector deserves to be exempted from the burden of these regulations - both for their value and for the controls that already surround them and the damage that has already been done. Global sectoral guidelines resulting from intense collaboration between industry and regulators are likely to deliver better results, and at lesser cost, than regulations that address chemicals indiscriminately and that are reminiscent of a Fortress Europe mentality emanating from bureaucrats in Brussels who appear to be disconnected from reality.

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Please note: the contact numbers given in the previous Hovione article (SCM, November 2002, pages 16-17) were incorrect. They should have been as below.

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